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FISH & RICHARDSON PC
P.O. BOX 1022
MINNEAPOLIS, MN 55440-1022

EXAMINER	
DEJONG, ERIC S	

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 07/26/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/058,655	BENIGHT ET AL.	
	Examiner	Art Unit	
	Eric S. DeJong	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 May 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-28* is/are pending in the application.

4a) Of the above claim(s) *18-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3-17* is/are rejected.

7)☒ Claim(s) *3* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1 sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED OFFICE ACTION

Withdrawal of Claim Objections

The previous objections to claims 11 and 17 are withdrawn in view of amendments made to the instant claims.

Claim Objections

Claim 3 is objected to under 37 CFR 1.75(c), as being of improper dependent form as the instant claim depends from a canceled claim. Applicant is required to cancel the claim, or amend the claim to place the claim in proper dependent form, or rewrite the claim in independent form. This objection is newly applied and necessitated by amendment.

For the purpose of continuing examination, the Examiner has construed that claim 3 is intended to depend from claim 1.

Withdrawal of Claim Rejections - 35 USC § 112, First Paragraph

The previous rejection of claims 1 and 6-17 under 35 USC § 112, first paragraph is withdrawn in view of applicants arguments.

Withdrawal of Claim Rejections – 35 USC §112, second paragraph

The previous rejection of claims 8, 11-15, and 17 under USC § 112, second paragraph is withdrawn in view of amendments made to the instant claims and applicants arguments.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 6, and 16 are rejected under 35 U.S.C. 102(e)(2) as being clearly anticipated by Agrafiotis et al. This rejection is maintained and reiterated from the previous Office Action.

The instant claims are drawn to a method of constructing a modular computational model for predicting one or more therapeutic properties of a chemical compound comprising obtaining a first data set describing an interaction, wherein the data set id obtained experimentally using a high throughput instrument, and using the first data set to construct a computer based first model to predict values describing the interaction between a chemical compound and a first interaction partner.

Instant claim 1 requires obtaining a set of data describing the interaction between each member of a set of training compounds and an interaction partner, along with data about chemical structure and/or physical properties, for use in constructing a module to predict values describing the interaction between a chemical compound and the interaction partner. Agrafiotis et al. teaches obtaining physical, chemical and/or biological data pertaining to selected compounds, as well as their related structural properties, for use in constructing and operating an iterative computational module to predict physical properties of a compound. See Agrafiotis et al., abstract.

The instant application discloses several biological examples of interacting molecules, however the definition put forth in the specification as to what the training compounds and interacting partners may be is summarized by the limitation that they are molecules known to interact with one another. Agrafiotis et al. provides a specific example embodiment of the disclosed invention involving thrombin binding to several inhibitors. See Agrafiotis et al., column 9, lines 7-33. This example demonstrates that selecting molecules known to interact with one another, such as the ligand-receptor pair embodied in inhibitor-thrombin binding, are suitable for use in the methods disclosed by Agrafiotis et al.

The instant application discloses construction of a module that predicts values describing the interaction between a compound and interaction partner consisting of one or more scoring functions that incorporate a set of data describing the interaction between training compound and interaction partner and may further incorporate the physical structure and/or physical properties of the compound. The iterative

computational module disclosed in Agrafiotis et al. incorporates data on selected compounds, for example a ligand-receptor pair, for use with one or more structure-property models, which the instant application discloses as a suitable type of scoring function, to predict properties that one or more compounds posses. See Agrafiotis et al. Column 11, lines 8-21. The predicted values returned by the module, as set forth in claim 1 must be of the same type of data as the data contained in the set of data used to construct the module. Agrafiotis et al. teaches that values returned by the iterative computational model may be of the type used in constructing the module. See Agrafiotis et al., column 13 line 65 to column 14 line 32. Amended claim 1 further requires that the first data set be obtained experimentally by a high throughput instrument. Though examples are included, the instant application does not provide a specific definition for a high throughput instrument. A reasonably broad interpretation of a high throughput instrument is an instrument that is designed to perform an automated series of experiments after being furnished with multiple samples. Agrafiotis et al. provides for alternative methods of analyzing and acquiring data for use in the invention that include manual, automatic or a combination of manual and automatic experimental means, the scope of which encompasses the above described definition of a high throughput instrument. See Agrafiotis et al. Column 9, lines 49-56.

Instant claim 6 requires the incorporation of a second data set, a second interaction partner and a second modular computational module for predicting therapeutic properties of a chemical compound. Instant claim 16 further requires the

incorporation of a third data set, a third interaction partner and a third modular computational model for predicting therapeutic properties of a chemical compound.

Agrafiotis et al. teaches an iterative method that allows for the repetition of the above described method steps in order to perform a second round of computational modeling to arrive at a prediction of properties for a given chemical compounds. See Agrafiotis et al. Column 52, lines 8-15 and Column 52, lines 27-29. The second round of computational modeling specifically allows for the use of different chemical compounds, a different specie of data describing the compounds, and a separate iterative computational module with regard to what was used in the first round of computational modeling. This allows for an embodiment of the invention where two, three or more separate rounds of modeling are performed by two, three or more computational modules to arrive at a prediction of properties on a set of chemical compounds.

Response to Arguments

Applicant's arguments filed 31 May 2005 have been fully considered but they are not persuasive.

Applicants assert that Agrafiotis et al. do not include the direct coupling of a high throughput property measuring instrument to a computational software package which transforms the collected data from the instrument into a model relating the measured properties to molecular features for designing new molecules. Applicants argument are not directed to the merits of the previously presented rejection. In the previous Office action page 7, lines 16-20 stated "(t)hough examples are included, the instant

application does not provide a specific definition for a high throughput instrument. A reasonably broad interpretation of a high throughput instrument is an instrument that is designed to perform an automated series of experiments after being furnished with multiple samples." As such applicants assertion that Agrafiotis et al. does not address or contradict this interpretation of the instantly claimed limitation of using a high through put instrument in the disclosure of Agrafiotis. Further, instant claim 1 does not recite the limitation of a "direct coupling of a high throughput property measuring instrument to a computational software package". Therefore applicants argument is not persuasive.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, ,148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3-6 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Agrafiotis et al. taken in view of Harrous et al. This rejection is maintained and reiterated from the previous Office action.

Agrafiotis et al. teaches the use of automatic experimental means to provide data describing interacting compounds, such as a ligand-receptor pair, but does not specify the use of multi-channel or multi-cell calorimeters or measurements of changes in enthalpy or a combination of changes in enthalpy, entropy and free energy in order to describe the interaction between two molecules.

Harrous et al. emphasizes the importance of selecting appropriate calorimetry instrumentation for investigations of molecular interactions in order to conserve materials and time (see Harrous et al.; page 97, first column, lines 6-13). Harrous et al. further specifies that energetic and kinetic studies must be used in complement to structural approaches in the characterization of biological macromolecules interacting

with molecules of low molecular weight (see Harrous et al.; first paragraph of the Introduction). As recited in the abstract, Harrous et al. discloses a study that evaluates the use of a Gill titration calorimeter and demonstrates its utility in determining changes in enthalpy, entropy and free energy and how combinations of these values are used in describing the interaction between with several inhibitors that bind to beta-trypsin, a well known protein enzyme. The Gill calorimeter is consistent with a reasonably broad interpretation of a multi-channel or multi-cell calorimeter as it provides an automated high-throughput experimental means of analyzing multiple samples and provides thermodynamic data on the interaction between molecules. See (Harrous et al.; page 96, column two, line 37 to page 97, column one, line 3),

Therefore it would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains to employ the methods taught by Agrafiotis et al. and incorporate the use of a multi-cell or multi-channel calorimeter to measure changes in enthalpy or a combination of the changes in enthalpy, entropy, and free energy in order to describe the interaction between a training compound and a first interaction partner because Harrous et al. teaches selecting appropriate calorimetry instrumentation for investigations of molecular interactions is useful to conserve materials and time.

Claims 1, 6, 7, 11, and 15-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Agrafiotis et al. taken in view of Korzekwa et al. This rejection is maintained and reiterated from the previous Office action.

Agrafiotis et al. teaches utilizing one or more iterative computational modules in order to predict potential property values related to interacting compounds, such as ligand-receptor pairs, but does not specify the prediction of therapeutic or ADMET property values nor suggest a preferred combination of properties predicted by a given set of modules.

Korzekwa et al. teaches that a bottleneck exists in the drug discovery process which begins with lead compound optimization and that a primary consideration for related investigations in the area of lead development is a compounds metabolic fate. On this point, Korzekwa et al. propose overcoming the bottleneck through the use of predictive models which focus on absorption, distribution, metabolism, excretion and other pharmacokinetic properties, the set of which encompass ADMET properties (absorption, distribution, metabolism, excretion, and toxicological) as disclosed in the instant application. See Korzekwa et al.; column 1, lines 34-65. Further, it is explicitly asserted that "...it would generally be difficult to predict the effect of structural modification of a target compound upon its metabolism by enzymes, given that the molecular mechanisms of its metabolism involve an intimate combination of effects contributed by the metabolizing enzymes and the compounds themselves" (Korzekwa et al.; column 5, lines3-8).

Therefore it would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains to predict the therapeutic, ADMET and/or combinations of these properties as taught by Korzekwa et al. in combination with the computational modules taught by Agrafiotis

because Korzekwa et al. teaches that predictive models which focus on absorption, distribution, metabolism, excretion and other pharmacokinetic properties, the set of which encompass ADMET properties, are useful as a primary consideration for related investigations in the area of lead compound development.

Claims 1, 6, 7, 8, 9, 11, and 15-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Agrafiotis et al. taken in view of Korzekwa et al. and Ekins et al. This rejection is maintained and reiterated from the previous Office action.

Agrafiotis et al. provides several embodiments of iterative computational modules that employ one of several varieties of QSAR model but does not specify the use of a 4D-QSAR model or that the model predict therapeutic property values. As discussed above, it would be obvious to one skilled in the art to predict therapeutic and/or ADMET property values using the iterative computational modules taught by Agrafiotis et al. taken in view of Korzekwa et al., but neither specify the use of a module that incorporates the use of a 4D-QSAR model.

Ekins et al., drawn to an investigation of the utility and quality of 3D- and 4D-QSAR models of Cytochrome P-450 3A4 inhibitors, suggests the importance of 4D-QSAR models for *in silico* prediction of properties describing interactions between molecules and asserts that in refining screening processes and accelerating drug discovery applicable computational techniques, such as the 4D-QSAR model, are required. See Ekins et al.; page 429, Abstract and column 1, first full paragraph.

Therefore it would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains incorporate a 4D-QSAR model as taught by Ekins et al. and Korzekwa et al. into the computational module taught by Agrafiotis et al. for use in the prediction of therapeutic property values related to the interacting compounds because Ekins et al. teaches 4D-QSAR models are greatly enhance and accelerate drug discovery in applicable computational techniques.

Claims 1, 6, 7, 9-11 and 15-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Agrafiotis et al. taken in view of Korzekwa et al. and Khiat et al. This rejection is maintained and reiterated from the previous Office action.

Agrafiotis et al. discloses a specific embodiment of the invention that involves the evaluation of inhibitors to the enzyme thrombin, a protein that serves as the interaction partner for a set of inhibitors, but does not disclose an embodiment of the invention where the interaction partner is a protein hormone or require that a module predict therapeutic property values. As discussed above, it would be obvious to one skilled in the art to predict therapeutic and/or ADMET property values using an iterative computational module taught by Agrafiotis et al. taken in view of Korzekwa et al., but neither specify the selection of an interaction partner which is a protein hormone.

Khiat et al. discloses that an initial structural analysis based on NMR constraints was insufficient in defining the interactions between a critical region of motilin, a protein hormone, with erythromycin A derivatives. Instead, an alternative structure-activity study

was performed and relied upon to establish the structure and properties of key functional groups within motilin that interact with inhibitor molecules. Further, no studies had been performed prior to Khiat et al. that relied on structure-activity comparisons with these specific compounds and protein hormone, suggesting that other investigations into protein hormone systems would benefit from similar structure-activity studies.

Therefore it would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains to combine the prediction of therapeutic property values related to the interacting compounds under investigation as taught by Khiat et al. and Korzekwa et al. with the computational module taught by Agrafiotis et al. because Khiat et al teaches that the disclosed alternative structure-activity overcomes inefficiencies encountered in previous studies of protein-hormone systems.

Claims 1, 6, 7, 11-13, and 15-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Agrafiotis et al. taken in view of Korzekwa et al. and Klein et al. This rejection is maintained and reiterated from the previous Office action.

Agrafiotis et al. provides several embodiments of iterative computational modules that employ one of several varieties of QSAR model but does not specify the use of an MI-QSAR model or that a module predict therapeutic property values. As discussed above, it would be obvious to one skilled in the art to predict therapeutic and/or ADMET property values using the iterative computational modules taught by Agrafiotis et al.

taken in view of Korzekwa et al., but neither specify the use of a module that incorporates the use of an MI-QSAR model.

Klein et al. discloses how intermolecular membrane-interaction descriptors were derived from molecular dynamics simulations of the compounds in a model phospholipid monolayer and analyzed with an MI-QSAR model. See Klein et al., abstract. Further, Klein et al. asserts that very few structure-activity stidues for explicit membrane-interactions are available to date and despite the many efforts that have been made to understand the molecular principles behind drug-phospholipid interaction. See Klein et al., Introduction, second full paragraph. This suggests that the MI-QSAR model is one of a very few structure–activity models capable of handling the demands of the many studies involving explicit membrane-interactions.

Therefore it would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains to use prediction of therapeutic and/or ADMET property values related to interacting compounds which involve explicit membrane-interactions as taught by Kleins et al. and Korzekwa et al. with an MI-QSAR model into the computational module taught by Agrafiotis et al. because Kleins et al. teaches that the MI-QSAR model is one of a very few structure-activity models capable of handling the demands of the many studies involving explicit membrane-interactions

Claims 1, 6, 7, 11, and 13-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Agrafiotis et al. taken in view of Korzekwa et al. and Oprea et al. This rejection is maintained and reiterated from the previous Office action.

Agrafiotis et al. discloses a specific embodiment of the invention that involves the evaluation of inhibitors to the enzyme thrombin, a protein that serves as the interaction partner for a set of inhibitors, but does not disclose an embodiment of the invention where the interaction partner is a membrane, membrane-like compound or a membrane that is part of a Caco-2 cell nor suggest predicting therapeutic and/or ADMET property values. As discussed above, it would be obvious to one skilled in the art to predict therapeutic and/or ADMET property values using the iterative computational modules taught by Agrafiotis et al. taken in view of Korzekwa et al., but neither specify the selection of an interaction partner which is a membrane, membrane-like compound or a membrane that is part of a Caco-2 cell.

Oprea et al. sites that "Poor intestinal permeability of drugs constitutes a major bottleneck in the successful development of candidate drugs" and that the pressure felt by current medicinal and combinatorial chemists drives researchers to incorporate a QSAR paradigm for drug absorption properties, as exemplified in their disclosure drawn to a structure-activity study that specifically involved a Caco-2 cell membrane. See Oprea et al.; Abstract.

Therefore it would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains to use computational module as disclosed in Agrafiotis et al. in predicting therapeutic property

values relevant to one or more ADMET property values as taught by Korzekwa et al. using Caco-2 membrane and membrane-like compounds as taught by Oprea et al. because Oprea et al. teaches that incorporating a QSAR paradigm of drug absorption properties overcomes a major bottleneck in the successful development of candidate drugs.

Response to Arguments

Applicant's arguments filed 31 May 2005 have been fully considered but they are not persuasive.

Applicants arguments directed to the inadequacy of Agrafiotis et al. are not persuasive for the reasons provided above. Further, Applicants assert that Harrous et al., Korzekwa et al, Ekins et al., Klein et al. and Oprea et al, do not suggest modification of Agrafiotis et al. that render obvious the instant claims. Applicants arguments do not address the provided motivational statements, as provided in the previous Office action and reiterated in the above discussion, and as such are not directed to the basis of the motivation to combine the cited references. Therefore, applicants arguments are not found persuasive.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry of a general nature or relating to the status of this application should be directed to Legal Instrument Examiner, Tina Plunkett, whose telephone number is (571) 272-0549.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric S. DeJong whose telephone number is (571) 272-6099. The examiner can normally be reached on 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, Ph.D. can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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EDJ

21 July 2005

JOHN S. BRUSCA, PH.D
PRIMARY EXAMINER